REMARKS

I. Introduction

Receipt of a final office action dated January 9, 2008 is acknowledged. In the action, the claims are rejected (1) for nonstatutory obviousness-type double patenting over claims 1-9 of U.S. Patent No. 5,851,999, and under (2) 35 U.S.C. § 103 as allegedly obvious over Lemischka (U.S. Patent 5,185,438) ("Lemischka"), Matthews et al., *PNAS*, 88:9026 ("Mathews") and Terman et al., *BBRC*, 187:1579 ("Terman"), in view of Ullrich et al., *Cell*, 61:203 ("Ullrich"), Ueno *et al.*, *Science*, 252:844 ("Ueno 1") and Ueno et al., *JBC*, 267:1470 ("Ueno 2"). The specification is also objected to for formality reasons.

II. Substance of the Interview

As an initial matter, Applicants wish to thank Examiner Spector for her time and courtesy extended by her during a July 31, 2008 telephonic interview with Applicants' representatives, Kristel Schorr and Galina Yakovleva. This response reflects the contents of the interview.

Specifically, during the interview Applicants presented arguments pertaining to the differing number of Ig domains in the family of receptors. The Examiner replied that it is the intracellular domain which is more important in the present invention, as there exist receptors having varying numbers of Ig domains but having similar properties upon truncation. The Matthews reference was also discussed, as well as the claim amendments presented herein.

III. Status of the Claims

Claim 5 is amended to recite a truncated Flk-1 "which inhibits the cellular effects of VEGF binding, wherein said truncated Flk-1 consists of an amino sequence corresponding to 1-806 of SEQ ID NO: 2". In addition, claim 6 is amended to more clearly state the invention. Exemplary support for the amended claims can be found throughout the specification, and in paragraph [0119] in particular.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested. Upon entry of these amendments, claims 5 and 6 will be pending. Applicants respectfully request reconsideration of these claims in view of the following remarks.

IV. Rejection of the claims under 35 U.S.C. §103

Claims 5-6 are rejected as being allegedly obvious over Lemischka (U.S. Patent No. 5,185,438), Matthews et al. ("Matthews") and Termen et al. ("Termen") in view of Ulrich et al. ("Ulrich") and Ueno et al. (including "Ueno-1" and "Ueno-2"). Applicants respectfully traverse this ground for rejection.

A. Lemischka

Lemischka describes Flk-1 and Flk-2 and references the Hanks article, which describes the presence of conserved amino acids in the catalytic domain of the family of receptor tyrosine kinases. Lemischka, however, states that Flk-2 is in a "new functional class" as compared to other receptor tyrosine kinases such as CSF and PDGF. Lemsichka then states that Flk-1 is in a different functional class based on expression in some more mature hematopoietic cells but does not state whether Flk-1 would be in the same class as CSF and PDGF.

B. Matthews

Although the Office states that the primary references, including Matthews, teach the relatedness of Flk-1 to other receptor tyrosine kinases, Matthews actually points out differences between Flk-1 and other receptor tyrosine kinases. Although Matthews indicates there are conserved cysteine residues, Matthews describes Flk-1 as being considerably larger than other family members and that Flk-1 has 7 Ig-like domains (others have 5).

Furthermore, Matthews states that while the kinase insert of Flk-1 contains potential sites for tyrosine kinase autophosphorylation, Flk-1 is distinct from c-kit, c-fms and Pdgfra/b because it lacks the consensus sequence for binding PI-3.

And lastly, Matthews states that "[i]nterestingly, Flk-1 appears to have seven immunoglobulin-like domains in its extracellular region, and together with Flt, may define an additional subfamily of receptor PTKs." This further highlights the differences between various receptor tyrosine kinases and underscores the inability to extrapolate Flk-1 function based on behavior of other receptor tyrosine kinases.

C. Terman

Terman describes the KDR receptor and structural similarities of KDR to Flk-1. Terman, however, does not disclose the similarity between Flk-1 and a receptor tyrosine kinase that has been truncated in the secondary references, such as the FGF or PDGF receptor. In other words, because Terman does not talk about the structural similarity between Flk-1 and one of the receptors that has been truncated, this reference does not "teach the relatedness of Flk-1 to the receptors discloses by the secondary references" (office action at 5). as indicated by the Office as being the essence of their rejection.

D. Ueno I

Secondary reference Ueno I describes a PDGF receptor lacking most of its cytoplasmic domain that can form heterodimers with a wild-type PDGF receptor and block WT receptor function. Ueno I, however, states that other truncated receptor tyrosine kinases (such as the EGFR and insulin receptor) inhibited wild-type receptor function but "did not inhibit the autophosphorylation of wild-type receptors and the mechanisms by which the kinase-defective mutants inhibited wild-type receptor function were not known. Ueno I at 847. Thus, even receptors within the family of receptor tyrosine kinases can function differently and by different mechanisms, further supporting the inability to predict function based solely on structural similarities.

In other words, although the truncated PDGFR dimerized with a wild-type PDGF receptor and interfered with cell signaling, the mechanism by which this occurred was distinct from that of the EGF receptor and insulin receptor truncations. As such, the mechanism of inhibition of the truncated PDGF receptor cannot be extrapolated to a different truncated

receptor tyrosine kinase. And similarly, a truncated PDGF receptor cannot predict the activity of other truncated receptor tyrosine kinases.

E. Ueno II

Ueno II discloses a truncated FGF receptor but as provided above, the FGF receptor is structurally different from Flk-1. For example, the FGF receptor does not have the 7 Ig-like domains characteristic of Flk-1, KDR, and other more similar receptor tyrosine kinases.

Furthermore, Ueno suggests that the wild-type FGFR and truncated FGFR heterodimers may activate the cytoplasmic signaling pathways differently than do the homodimers of the truncated FGFs. Accordingly, the mechanism of inhibition may again be different, even between truncated FGFs, depending on whether homo- or heterodimers are formed, which supports the position that structural similarity does not absolutely predict function.

F. Ullrich

Ullrich is simply a review article that describes EGF, PDGF, IGF-1 and CSF as a family of receptor tyrosine kinases but does not mention Flk-1 or its other more structurally similar receptor tyrosine kinases. As such, the combination of Ullrich with the primary references and/or the other secondary references does not teach each and every element of the claimed invention.

* * *

In the interest of expediting prosecution, Applicants amended the claims to refer to a cell line that comprises a recombinant vector comprising a nucleotide sequence that encodes a truncated Flk-1 that consists of an amino sequence corresponding to 1-806. This particular Flk-1 truncation contains the extracellular and transmembrane domains of Flk-1, and 23 amino acids from the cytoplasmic domain. Although the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.* 127 S.Ct. 1727 (U.S. 2007) indicated that a "finite number of identified, predictable solutions" may lead to a product "not of innovation but of ordinary skill and common sense" (*KSR*, 127 S.Ct. at 1742), the ability to delete up to about 584 residues in the

C-terminal domain of Flk-1 is not a "finite number." Additionally, there is no guidance in the cited art to retain 23 amino acid residues of the cytoplasmic domain either.

Furthermore, the obviousness inquiry must rely on evidence available at the time of the invention. See *Eisai Co. Ltd. and Eisai, Inc. v. Dr. Reddy's Laboratories, Ltd., Dr. Reddy's Laboratories, Inc., and Teva Pharmaceuticals USA, Inc.*, --F.3d--, 2008 WL 2791884 (Fed. Cir. 2008), *citing Takeda Chem. Indus. v. Alapharm Pty.*, Ltd.,, 492 F.3d 1350 at 1356 (Fed. Cir. 2007). And in 1992, the priority date of the present invention, Flk-1 had only just been identified (as evidenced by Lemischka) and the similarity between the VEGF and PDGF systems had not yet been characterized (Terman at 1585). Thus, the level of a person of ordinary skill in the field of Flk-1 receptor tyrosine kinases at the time of filing the present application was low.

Lastly, the court in *Eisai* stated that "[t]o the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai*, at 4. As with the chemical arts, biotechnology is often unpredictable as well.

Taken together, none of the cited references, either alone or in combination, would suggest making the presently claimed truncated Flk-1, which retains 23 residues in the cytoplasmic domain, even in view of *KSR*.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

Applicants believe that the present application is now in condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this submission, or should any issue remain, the Examiner is invited to contact the undersigned by telephone in order to advance prosecution.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date Aug 29, 2008

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5475
Facsimile: (202) 672-5399

Michele M. Simkin
Attorney for Application
Registration No. 34,717